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| APPLICATION NO.                                                                                       | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.           | CONFIRMATION NO. |
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| 10/734,730                                                                                            | 12/15/2003  | Jo Klaveness         | NIDN-10314                    | 1951             |
| 7590 01/03/2007<br>Li CAI<br>Amersham Health, Inc.<br>101 Carnegie Center<br>Princeton, NJ 08540-6231 |             |                      | EXAMINER<br>SCHLIENTZ, LEAH H |                  |
|                                                                                                       |             |                      | ART UNIT<br>1618              | PAPER NUMBER     |
| SHORTENED STATUTORY PERIOD OF RESPONSE                                                                |             | MAIL DATE            | DELIVERY MODE                 |                  |
| 3 MONTHS                                                                                              |             | 01/03/2007           | PAPER                         |                  |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/734,730

Applicant(s)

KLAVENESS ET AL.

Examiner

Leah Schlientz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-36 and 39-60 is/are pending in the application.
- 4a) Of the above claim(s) 1-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 31-36 and 39-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☒ Certified copies of the priority documents have been received in Application No. 08/959,206.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                                                     |                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                                                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                                | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>12/15/2003</u> . | 6) <input type="checkbox"/> Other: _____                                                |

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**DETAILED ACTION*****Election/Restrictions***

Applicant's election without traverse of Group II in the response filed 11/6/2006 is acknowledged. The election of the following species is also acknowledged: perfluorobutane as gas, phosphatidylserine as stabilizing agent, dipalmitoyl-KRKR and WQPPRARI as vectors, atenolol as therapeutic agent. Claims 1 – 36 and 39 – 60 are pending. Of the above listed claims, claims 1 – 30 have been withdrawn from consideration as being drawn to a non-elected Group.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31 and 35 – 60 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38 - 44 of copending Application No. 10/722,075. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to diagnostic agents comprising a suspension of a reporter comprising gas containing material in an aqueous carrier liquid, wherein the gas comprises a halogenated low molecular weight hydrocarbon, the surfactant is a phospholipid, and the agent is coupled to one or more vector molecules. For example, the specific agent of claim 38 of 10/722,075 is anticipatory of the generic agent of instant claim 31. Both agents may further comprise a therapeutic compound.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 31 –36 and 39 – 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 17 of U.S. Patent No. 6,264,917. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to targetable contrast agents comprising a suspension in an aqueous carrier liquid a reporter comprising gas-filled microbubbles stabilized by film-forming surfactant further comprising at least one vector. Both sets of claims are comprise the administration of a substance which releases the microbubbles from the target. As such, the claims are overlapping in scope and are obvious variants of one another.

Claims 31 and 35, 36, and 39 – 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 22 of U.S. Patent No. 6,261,537. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to targetable contrast agents comprising a suspension in an aqueous carrier liquid a reporter comprising gas-filled microbubbles stabilized by film-forming surfactant, wherein the surfactant comprises phospholipids and further comprising at least one vector. For example, the specific agent of claim 1 of 6,261,537 is anticipatory of the generic agent of instant claim 31.

### ***Specification***

The disclosure is objected to because of the following informalities: the specification contains drawing(s) on page 146 which are not permitted. Graphical illustrations, diagrammatic views, flowcharts, and diagrams in the descriptive portion of the specification do not come within the purview of 37 CFR 1.58(a), which permits tables and chemical formulas in the specification in lieu of formal drawings. The examiner should object to such descriptive illustrations in the specification and request formal drawings in accordance with 37 CFR 1.81 when an application contains drawings in the specification. These drawings must be deleted from the specification, but may be filed as "drawings" as stated above. Applicant is reminded that the specification must include a "Brief Description of the Drawings" if the application contains any drawings.

Applicant is also advised that the substitute specification should include all of the amendments made to the specification, e.g., addition of sequence pages and sequence ID numbers, etc.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

### ***Claim Objections***

Claim 60 is objected to because of the following informalities: the claim lacks punctuation at the end of the sentence. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31 – 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnostic agents having a specific reporter

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material, such as microbubbles of DSPS with specific combinations of vectors, such as binding peptides, KRKR and WOPPRARI, does not reasonably provide enablement for methods wherein the diagnostic and/or therapeutic agent comprises any reporter comprising gas-containing or gas-generating material wherein said reporter being capable of forming at least two different types of binding pairs with a target as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In particular, the specification fails to enable the skilled artisan to practice the invention without undue experimentation. As held by *Ex parte Forman* (230 USPQ 546, BDPatApp & Int.) and *In re Wands* (8 USPQ 2d 1400, CAFC), there are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation.

Amount of guidance present

The specification fails to provide the requisite guidance for enabling the scope of the invention. The guidance provided is directed to specific types of reporters comprising a gas-containing or gas-generating material, but does not provide guidance for the scope as claimed. Since the reporter is any gas-containing or gas-generating material, the claim encompasses an almost unlimited number of possibilities for the reporter. The vector also encompasses an almost unlimited number of targeting agents (e.g. various types of biomolecules, etc.). However, the specification fails to provide the requisite guidance of how to bind the vectors to the various types of reporters

encompassed by the instant invention, all of which are distinct and have different binding and conjugating properties which would require undue experimentation to bind a vector or vectors thereto. Also, the specification fails to provide the requisite guidance on what combinations of the following are useful, 1) reporters and vectors, e.g. how many different types, what types with what reporters, etc. and 2) what types of vector combinations are possible with any given reporter, e.g. antibodies with small peptides, etc.

Absence of working example

The specification fails to provide any working examples relating to the scope of the invention but only provides examples of specific reporter and vector combinations, e.g., microbubbles with DSPS with specific combinations of vectors, such as, binding peptides KRKR and WOPPRARI.

Nature of the invention

The nature of the invention is a method of generating enhanced images of a human or non-human body using an agent which comprises a suspension in an aqueous carrier liquid of a reporter comprising gas-containing or gas-generating material, said agent being capable of forming at least two types of binding pairs with a target. For such an invention the skilled artisan must be given guidance on what reporters may be used and what combinations of vectors may be employed therefor. Given the use as *in vivo* agents, it is imperative that sufficient guidance is provided so that the agents are useful as diagnostic and/or therapeutic agents, e.g. what types of vector combinations may be used with what reporter(s), as well as, how they are



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conjugated thereto. Without specific guidance, it would require undue experimentation to find what types of gas-containing or gas-generating materials, e.g., which include microbubbles, microballoons, liposomes, liquid emulsions, gas emulsions, solid particles, etc. would be useful with what combination of vectors, e.g., which include various biomolecules, e.g. antibodies, peptides, small-molecule antagonists, carbohydrates, genetic material, etc. The nature of a diagnostic and/or therapeutic method requires a certain degree of guidance to specify what is useful because of the inherent unpredictability of an *in vivo* method.

#### State of the prior art

The state of the prior art using any reporter having conjugated thereto more than one vector with any reporter having conjugated thereto more than one vector with any reporter comprising a gas-containing or gas-generating material is not well understood. The use of more than one vector, which binds to different targets on the same or different cells, further complicates the method since the use of two or more different vectors for specific targeting is not well recognized, for apparent reasons, e.g. the targeting would not be specific as two different sites would be targeted which may not be in a close approximation to allow for binding of the reporter thereto.

#### Relative skill of those in the art

The relative state of those in the art would not enable the skilled artisan to practice the invention because he or she would be faced with insurmountable experimentation in conjugating two or more different vectors which bind to two or more different targets on the same or different cells. Because of the great number of possible

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reporters, the skilled artisan would not know what combinations are useful. The skilled artisan would have to first choose a specific type of reporter comprising a myriad of different gas or gas-generating materials, and then find what two or more vectors may be conjugated thereto (as well as, how they are conjugated thereto), to yield a useful diagnostic and/or therapeutic agent.

#### Unpredictability in the art

Given the diversity of the reporter as claimed, the vector as claimed (e.g. more than one type of different vectors), as well as, the inherent predictability of targeted *in vivo* diagnostic and/or therapeutic agents and the use of such agents of the instantly claimed scope would be very unpredictable and would require undue experimentation. For example, the skilled artisan would be faced with the unpredictability of combining more than one type of vector on a reporter (e.g. usually a small gas-containing particle) because of known biochemical interactions, such as steric hindrance, loss of activity of one or more vectors, binding interactions with the reporter and/or with other vectors, etc. The skilled artisan would expect that binding any vector to any reporter containing gas-containing or gas-generating material would be chemically difficult without specific guidance, and that such binding may cause loss of activity of one or more of the vectors. Given the inherent unpredictability of the art of *in vivo* targeting, especially of binding more than one type of vector to a reporter, for administration to a patient, it would be very unpredictable to make and use the agents which are commensurate in scope with the instant claims.

#### Breadth of the claims

The claims are very broad, wherein the agent comprises a reporter comprising any gas-containing or gas-generating material (e.g. an almost unlimited number of possibilities) which is conjugated to more than one type of vector (e.g. also an almost unlimited number of possibilities), which is amplified because of the various possible combinations of reporters and vectors, as well as vector subcombinations.

It is suggested that the instant method claims, which are directed to a method of generating enhanced images of a human or animal body which comprises administering to said body an agent and generating an ultrasound, MR, x-ray, radiographic or light image of at least a part of the body, be amended to reflect the prosecution of the related product claims directed to a targetable diagnostic and/or therapeutically active agent in parent case 08/959,206, now patent 6,331,289. Claim 31 could be more favorably considered were the agent amended to similar to the following: "wherein said agent comprises a suspension in an aqueous carrier liquid of a reporter comprising gas-containing material in the form of phospholipid-stabilized gas microbubbles, said reporter being conjugated to more than one type of vector, the vectors binding to different targets on the same or different cells," (i.e. the limitations of parent case 6,331,289).

Claim 49 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for various specific vectors, including dipalmitoyl-KRKRWQPPRARI, etc., does not reasonably provide enablement for "and pieces

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thereof" (pertaining to peptide hormones), molecules generated from combinatorial libraries, and small bioactive molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In particular, the specification fails to enable the skilled artisan to practice the invention without undue experimentation. As held by *Ex parte Forman* (230 USPQ 546, BdPatApp & Int.) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), there are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. In the instant case, without some definition or description of such vectors, one skilled in the art cannot practice the invention because it would require undue experimentation to determine what works. The specification provides no guidance for making or using molecules from a piece of a peptide hormone, a combinatorial library, or a small bioactive molecule. The claims are very broad, covering a vast number of vectors which may bind to various biological molecules, in that, a piece of a peptide hormone may encompass any part of such a peptide or any molecule from the almost unlimited potential of combinatorial libraries. There is very little predictability in the art concerning targeting agents which are derived from any piece of a peptide hormone, any compound from a combinatorial library, or any small bioactive molecule. Most often cited in the art a specific known targeting moiety (e.g. a known antibody, etc.) is used to increase the effective targeting of the agent. The skilled artisan would not expect random compounds from a piece of a hormone (which

may include any "piece" thereof), or from a combinatorial library, or any small molecule to effectively act as a targeting vector or to be properly conjugated to the microbubbles of the instant invention. Further, it would require undue experimentation to prepare such vectors, given the lack of guidance of these types of vectors in the instant disclosure. The specification fails to provide guidance or any working examples for the claimed agents wherein the vector is a piece of a hormone, a molecule from a combinatorial library, or a small bioactive molecule. No specific vectors within the scope of such groups are described in the specification. Because of the lack of guidance as stated hereinabove, it would require an artisan to perform undue experimentation in order to first determine which "pieces" of hormone, small bioactive molecule, or molecule from a combinatorial library can be prepared and then which of these may be used in the agents instantly claimed for the disclosed utility.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 – 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is drawn to a method as claimed in claim 31 which comprises the steps i) administering to said body a pre-targeting vector, and thereafter ii) administering an agent, said agent comprising a vector having affinity for said pre-targeting vector. The claim is confusing because it is unclear whether or not the agent administered in step

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"ii" is the same agent which is administered in claim 31. It is also unclear whether the steps in the method of claim 32 are steps which are practiced *in addition* to the step of claim 31, wherein an agent is administered to a body, or whether step "ii" of claim 32 is a repetition of the same step of administering an agent as in claim 31.

Claim 34 is drawn to a method as claimed in claim 31 which comprises the steps i) administering to said body an agent, and thereafter ii) administering a substance capable of displacing the agent from its target. The claim is confusing because it is unclear whether or not the agent administered in step "i" is the same agent which is administered in claim 31. It is also unclear whether the steps in the method of claim 34 are steps which are practiced *in addition* to the step of claim 31, wherein an agent is administered to a body, or whether step "i" of claim 34 is a repetition of the same step of administering an agent as in claim 31.

Claims 39 – 41, 44, 45, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39 – 41, 45, and 49 are vague because the use of the word "comprising" in the "Markush" groups is improper. *Ex parte Markush* sanctions claiming a genus expressed as a group consisting of certain specified materials, however, it is improper to use the word "comprising" instead of "consisting of." *Ex parte Dotter*, 12 USPQ 382 (Bd. App. 1931).

Claim 45 recites the limitation "the film-forming surfactant" in lines 1 – 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 45 is dependent upon claim 43, which is drawn to a method wherein the surfactant comprises at least one phospholipids. The method in claim 43 (and the independent claim upon which it is dependent) does not require that the surfactant is a film-forming surfactant.

Claim 57 – 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 57 is drawn to "a method as claimed in claim 31 further comprising a therapeutic compound." The claim is confusing because it is unclear regarding the step which is to be performed in the method. For example, it is unclear whether or not the therapeutic compound is comprised within the agent which is administered to a body or if the therapeutic compound is administered in a separate step in addition to the administration of the agent.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31 – 36 and 39 – 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (US 5,656,211), Schneider (US 5,643,553), Grinstaff (US 5,498,421), Quay (EP 727225) and Lanza (US 5,690,907).

The instant claims appear to be directed toward a method of generating enhanced images of a human or non-human body which comprises administering to said body an agent, wherein the agent comprises an aqueous suspension of gas-filled microbubbles (a reporter) stabilized by a film-forming surfactant, wherein the agent further comprises a vector (i.e. a targeting molecule). The claims further appear to limit



the gas to perfluorocarbons, etc. the vector to various targeting molecules (e.g. antibodies, etc.), and the surfactants to various lipids (e.g. phospholipids, etc.). The agent may further comprise a therapeutic agent.

Unger discloses a diagnostic and/or therapeutic agent comprising gas-filled vesicles (i.e. microbubbles) which are used for ultrasound imaging. The microbubbles are stabilized by one or more monolayers of lipid surfactants, see column 4, lines 30+. The vesicles (or bubbles) may comprise various targeting agents (or vectors), including antibodies, peptides, proteins, etc. (column 6, lines 1 – 27). The lipids may be conjugated to various polymers, such as polyamino acids, etc. (i.e. lipoproteins), see column 6, lines 12 – 28. The targeting agents may be attached to the vesicles in a variety of ways, for example, by specific chemical bonds (covalently) or through electrostatic interaction (column 6, lines 22 – 27). The vesicles may comprise various surfactants in a wide range of amounts within the scope of the instant claims, such as phospholipids (i.e. phosphatidylserines, etc.) (column 6, lines 28+). The gas may be selected from various gases within the scope of the instant claims, such as, perfluorocarbons, etc., for use in ultrasound imaging, see columns 13 – 14. The vesicles may further comprise various therapeutic and/or diagnostic agents (spin labels, etc.), see column 11, lines 21+.

Schneider discloses a gas-filled diagnostic and/or therapeutic agent (i.e. microbubbles) for ultrasonic imaging. The microbubbles may contain various surfactants, such as a microbubble shell-forming phospholipid, or more specifically phosphatidylserine, as well as polymeric surfactants, such as polyoxyethylene

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surfactants (column 6, lines 25 – 64). Schneider further teaches that targeting ligands (e.g. polypeptides, antibodies, etc.) may be bound to the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (column 9, lines 10+). Schneider further teaches that the microbubbles may comprise various diagnostic agents, including radioactive gas, etc. (column 9, lines 38 – 43).

Grinstaff discloses a diagnostic and/or therapeutic agent comprising polymeric shells which encapsulate gas (i.e. gas-filled microbubbles) which are used for *in vivo* drug delivery and for ultrasound and MR imaging, see column 7-8, abstract, claim 30. The gas may be selected from various perfluorocarbons within the scope of the instant claims, see columns 28 – 30. Grinstaff teaches that the polymeric shell may be modified to include suitable agents, such as phospholipids, which would inherently be in the form of a monolayer or coating (column 12, lines 15+). The polymeric shells may further comprise various polymers (such as polyalkylenes, as well as proteins for targeting (e.g. antibodies, enzymes, etc.), and a combination thereof. These targeting agents may be attached to the shell via an optional covalent bond (column 12, lines 15+). Grinstaff specifically teaches that the conjugation of a targeting moiety to the polymeric shell provides the advantage of site-specific delivery of the diagnostic or therapeutic agent (column 40). Grinstaff also teaches that the microbubbles may comprise various therapeutic agents (see columns 13 – 14). The therapeutic agent is coupled to the polymeric shell via disulfide bonds (see columns 9 – 10 and claims 6 –

8). A reducing agent (mercaptoethanol) may be administered which liberates a therapeutic agent (i.e. taxol) (example 9).

Quay discloses compositions comprising a diagnostic and/or therapeutic agent comprising an aqueous suspension of gas-filled microbubbles (a reporter) stabilized by a film-forming surfactant, wherein the agent further comprises a vector (i.e. a targeting molecule) (abstract and page 3+). Quay teaches that the microbubbles may comprise various surfactants and may be conjugated to various targeting molecules (e.g. antibodies, etc.) to provide the advantage of increased microbubble stability and site-specificity, respectively (see pages 4 – 8). Quay further teaches that the gas bubbles may comprise various gases, such as perfluorocarbons, etc. (page 9, lines 2 – 4).

Lanza discloses a diagnostic and/or therapeutic agent comprising an aqueous suspension of lipid encapsulated particles which may encapsulate various gases, such as nitrogen, oxygen, carbon dioxide, fluorocarbon, etc. (column 4, column 6, lines 57 – 62). Lanza discloses that the surfactant layer is an encapsulating lipid monolayer (column 8, lines 40 – 41). Thus, the particles are in the form of microbubbles (a reporter) which is stabilized by a monolayer of a film-forming surfactant (a lipid). Lanza teaches that the surfactants may be selected from various lipids, such as phospholipids, cholesterol, etc. (column 5, lines 40+). The gas-containing emulsion may be conjugated to biotin (a vector), which is administered in conjunction with a pre-targeting vector (avidin) (i.e. claim 1) or an antibody bound to avidin (ex. 5). Lanza further discloses that the particles comprise various diagnostic and/or therapeutic

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agents (column 7, lines 48+). The conjugate is effective for imaging by x-ray, ultrasound, magnetic resonance or positron emission tomography (abstract).

Since Unger, Grinstaff, Schneider, Quay, and Lanza all disclose compositions comprising targeted, lipid-coated microvesicles for *in vivo* delivery of diagnostic/therapeutic agents, they may be viewed as being in the same field of endeavor. Further, all disclose the need to attach site-specific ligands to microvesicles for methods of diagnosis or therapy.

Although Unger, Grinstaff, Schneider, Quay and Lanza may not specifically disclose microbubble compositions comprising all of the same surfactants, gases, vectors, and/or therapeutic agents claimed, it would have been obvious to one of ordinary skill in the art to prepare and use such compositions in methods of ultrasound imaging because Unger, Grinstaff, Schneider, Quay, and Lanza all teach that 1) microbubbles may be bound with various ligands (e.g. peptides, etc.) by various means of attachment to provide the advantage of targeting, 2) they may include various surfactants to provide increased stabilization, 3) they may include various diagnostic and/or therapeutic agents for methods of imaging and treatment. One of ordinary skill in the art would have been motivated to employ any of the materials taught in the prior art for preparing such microbubble-containing diagnostic or therapeutic agents in order to optimize such microbubbles and/or to treat/diagnose a variety of conditions.

It is noted that the instant claims do not *require* multiple vectors. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed.

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Cir. 1993). The instant claims are not limited to microbubbles having multiple vectors, but to an agent "*capable of* forming at least two types of binding pairs with a target." This may be accomplished by employing at least two vectors or one vector capable of binding to at least two sites, see instant claim 47. The recitation of "antibodies" by Unger, Schneider, Grinstaff, Quay, and Lanza would encompass various known antibodies, such as bi-specific or polyclonal antibodies which would be expected to be capable of forming at least two types of binding pairs with a target, as instantly claimed. For example, Quay specifically teaches "polyclonal antibodies" (page 8, line 34) and Grinstaff also teaches the use of polyclonal antibodies (example 12, column 39). Also, Unger discloses that a wide variety of such agents, which would encompass two or more vectors. Grinstaff teaches that various targeting agents and combinations thereof may be conjugated to the microbubbles, which would clearly encompass two or more vectors. Additionally, Lanza discloses microbubbles having a targeting ligand and a biotin (or avidin) activating agent, therefore, the microbubbles have two vectors (i.e. the targeting ligand (which may be various antibodies, lectins, peptides, etc.) and biotin (which binds avidin as the target). Furthermore, it has been held that such a recitation of an element "capable of" (as instantly claimed in claim 31) performing a function is not a positive limitation in any patentable sense. See *In re Hutchison*, 69 USPQ 138. Since the various targeting agents disclosed by the prior art would inherently be "capable of" binding to two or more sites, such agents are within the scope of the instant claims.

It is suggested that the instant method claims, which are directed to a method of generating enhanced images of a human or animal body which comprises administering to said body an agent and generating an ultrasound, MR, x-ray, radiographic or light image of at least a part of the body, be amended to reflect the prosecution of the related product claims directed to a targetable diagnostic and/or therapeutically active agent in parent case 08/959,206, now patent 6,331,289. Claim 31 could be more favorably considered were the agent amended to be similar to the following: "wherein said agent comprises a suspension in an aqueous carrier liquid of a reporter comprising gas-containing material in the form of phospholipid-stabilized gas microbubbles, said reporter being conjugated to more than one type of vector, the vectors binding to different targets on the same or different cells," (i.e. the limitations of parent case 6,331,289).

### ***Conclusions***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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